UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/801,540 | 03/08/2001 | Adrian Bot | A30571-A-PCT/USA-A | 7183 |

7590 06/19/2008

BAKER BOTTS L.L.P.
44TH FLOOR
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112-4498

| EXAMINER | |
|---|---|
| SGAGIAS, MAGDALENE K | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 06/19/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/801,540 | BOT ET AL. | |
| | Examiner | Art Unit | |
| | MAGDALENE K. SGAGIAS | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Applicant's arguments filed 3/17/08 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-2 are pending and under consideration. Claim 3 has been canceled.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Assateerawatt et al, [Asian Pacitic Journal of Allergy and Immunology, 11: 85-91, 1993 (IDS)] in view of Donnely et al, [Journal of Immunological Methods, 176: 145-152, 1994 (IDS)].

Assateerawatt et al, teach the immunogenicity and efficacy of a recombinant DNA Hepattis B vaccine, GenHevac B Pasteur in high risk neonates born from HBsAg and HBeAg positive mothers, school children and healthy adults (title). Assateerawatt et al, teach the inoculation of infants “group B” with hepatitis B protein antigens using the recombinat hepatitis B vaccine, GeneHevac B Pasteur, containing pre S1, pre S2 and S proteins at birth, 1, 2 and 12 months of age (p 86, 1st column, lines 1-8, and 2nd column, abstract)). Assateerawatt et al, teach also the inoculation of infants ‘group B) with the hepatitis B immunoglobulin (HBIG) (p 86, 2nd column). Assateerawatt et al, teach the protective efficacy of gorup A and B were 95.5% and 89.8% respectively, with no statistical significant difference (abstract). Assateerawatt et al,

teach the antibody titer declined gradually in both groups (p 87, 3rd column bridge to p 88). Assateerawatt et al, also discusses a very important probelm in the control and especially te helimination of hepatitis B virus is the duration of immunity and the necessity to booster immunization (p 90, 2nd column last paragraph). Assateerawatt et al, differs from the present invention for not teaching a naked DNA hepatitis vaccine.

However, at the time of the present invention Donnelly et al, teach immunization with naked DNA which induces both antibody and cell-mediated immune response which can serve as an alterantive to immunization with attenuated viruses (abstract and entire document). Donnelly discuses methods for inducing immune responses with DNA including hepatitis B virus surface antigen (HBsAg) (p 147, 2nd column last pragraph bridge to p 148). Donnelly concludes immunization with DNA is a simple, robust and effective means of eliciting both antibody and cell-mediated immune responses against viral proteins that is at least equivalent to that produced by immunization with conventional methods (p 150, 2$^{nd}$ column under conclusion). As such, Donnely provides sufficient motivation for one ordinary skil in the art to apply a DNA hepatitis B virus surface antigen (HBsAg) vaccine in the neonates of Assateerawatt et al.

Accordingly, in view of the teachings of Donnelly et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to apply a DNA hepatitis B virus surface antigen (Bag) in a neonates at birth or 1 month of high risk neonates born from HBsAg positive mothers with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Donnelly concludes immunization with DNA is a simple, robust and effective means of eliciting both antibody and cell-mediated immune responses against viral proteins that is at least equivalent to that produced by immunization with conventional methods.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicants argue that the Examiner has failed to establish a prima facie case of obviousness. As conceded by the Examiner, Assateerawatt does not teach or suggest immunization with a naked nucleic acid. Donnelly discloses various DNA immunizations across animal models having various target antigens, with an emphasis on viral target antigens. However, Donnelly is silent with respect to immunization of an infant human. Further, Donnelly states that "[t]he therapeutic uses of DNA vaccines are beginning to be explored," and "[t]he extent to which this method [of immunization with DNA] can be applied to proteins not of vertebrate origin, e.g., antigens from bacteria and protozoan parasites, remains to be determined." In view of the lack of teaching of immunization of an infant human, the limited knowledge regarding the therapeutic uses of DNA vaccines, and the limited application of immunization with DNA, one skilled in the art would not have been motivated to combine Assateerawatt with Donnelly with a reasonable expectation of success to immunize an infant human with a naked nucleic acid. As Assateerawatt and Donnelly, considered separately or in combination, do not teach or suggest immunization of an infant human with a naked nucleic acid.

These arguments are not persuasive because Assateerawatt does not teach immunization with a naked nucleic acid however Donnelly teaches immunization with naked DNA which induces both antibody and cell-mediated immune response which can serve as an alterantive to immunization with attenuated viruses. Donnelly discuses methods for inducing immune responses with DNA including hepatitis B virus surface antigen (HBsAg). Donnelly concludes immunization with DNA is a simple, robust and effective means of eliciting both antibody and cell-mediated immune responses against viral proteins and as such, Donnely

provides sufficient motivation for one ordinary skill in the art to apply a DNA hepatitis B virus surface antigen (HBsAg) vaccine in the neonates of Assateerawatt et al. Assateerawatt et al teach immunizations of humans as is required in the instant invention. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Donnelly concludes immunization with DNA is a simple, robust and effective means of eliciting both antibody and cell-mediated immune responses against viral proteins that is at least equivalent to that produced by immunization with conventional methods. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Assateerawatt et al, (Asian Pacitic Journal of Allergy and Immunology, 11: 85-91, 1993 (IDS)) in view of Donnelly et al, (Journal of Immunological Methods, 176: 145-152, 1994 (IDS)) and further in view of **Chisari et al,** (Springer Semin Immunopathol, 17: 261-282, 1995).

The 103 rejection of claim 1 as being unpatentable over Assateerawatt et al, taken with Donnelly et al, is applied as indicated above.

Assateerawatt et al, taken with Donnelly et al, do not teach an inclusion of more than one relevant epitope of one or more target antigens associated with the pathogen.

However, at the time of the present invention **Chisari et al,** teach clonal deletion of HBV-specific T cells as a consequence of transplacental infection of the developing fetus, or transplacental passage of sub viral antigens could play an important role in the chronic infection that develops in neonates born to infected mothers (p 271, under neonatal tolerance).

Alternatively, postnatal infection may induce a weak and defective HBV-specific immune response because of the immunological immaturity of the newborn infant, although this is less attractive since it is well known that newborn infants respond quite well to immunization with **HBsAg**. Therefore, it is likely that transplacental infection or passage of soluble and/or particulate viral antigens contribute substantially to viral persistence in the infected neonate. In line with this possibility, it has been shown that nontransgenic progeny of **HBeAg**-positive transgenic mothers are tolerant to both HBeAg and HBcAg at the T cell level, presumably due to the thymic deletion of MHC class II-restricted HBV nucleocapsid-specific helper T cells as a result of transplacental exposure to HBeAg. Since intrauterine infection of the fetal liver by HBV has been described by many investigators, it is likely that not only tolerance to HBV nucleocapsid antigens but also to the other viral proteins can contribute to viral persistence by negative selection of the responding cells in the thymus during fetal development. Interestingly, neonates born to HBeAg-positive mothers are effectively protected against HBV infection when immunized with the HBsAg vaccine even though their immune system may have been exposed to HBV envelope antigens during its maturation. This suggests that neonates are immunocompetent with respect to this (HBsAg) antigen and that HBV envelope-specific T and B cells are still present and functional. This may indicate that tolerance to HBV envelope antigens is not induced in this setting or that exposure to viral proteins during fetal life does not result in a permanent state of tolerance if non-responsiveness can be reversed by HBsAg immunization (p 271, under neonatal tolerance). As such, Chisari et al provide sufficient motivation for one of ordinary skill in the art to apply the HBeAg to the HBsAg DNA vaccine of Assateerawatt et al and Donnelly et al.

Accordingly, in view of the teachings of Chisari et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the HBsAg

DNA vaccine of Assateerawatt et al and Donnelly et al by use of HBeAg relevant epitope for inducing a T cell response in high risk neonates born from HBsAg and HBeAg positive mothers, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Chisari et al suggests that neonates born to HBeAg-positive mothers are effectively protected against HBV infection when immunized with the HBsAg vaccine and that HBV envelope-specific T and B cells are still present and functional, particularly since Assateerawatt et al, noted that infants serum samples of the vaccinated neoantes tested for HBsAg antibody titer declined gradually by use of the protein vaccine and moreover since Donnelly teaches that DNA vaccines induce both humoral and cellular immune response.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicants argue that the Examiner has failed to establish a prima facie case of obviousness. First, the statement by Chisari regarding infants born to HBeAg-positive mothers cites Beasley, but Chisari misinterpreted Beasley, which was cited to support the proposition that "neonates born to HBeAg-positive mothers are effectively protected against HBV infection when immunized with the HBsAg vaccine." Chisari, p. 272. Contrary to Chisari's interpretation, Beasley et al. (Hepatology 3:135-141, 1983; abstract attached as Exhibit A) reports an efficacy trial of hepatitis B immune globulin ("HBIG") for prevention of the mother-to-infant transmitted HBsAg carrier state by monitoring the carrier rate of infants given HBIG, which is neither a HBsAg vaccine nor a naked nucleic acid. Beasley, abstract. Second, although Chisari does state that "it is well known that newborn infants respond quite well to immunization with HBsAg," Chisari does not teach or suggest immunization of neonates with a naked nucleic acid. Further, as set forth above, Assateerawatt and Donnelly, considered separately or in combination, do not

teach or suggest immunization of an infant human with a naked nucleic acid. Therefore, Assateerawatt, Donnelly and Chisari, considered separately or in combination, do not teach or suggest the subject matter of claims 1-2.

These arguments are not persuasive because Chisari teaches neonates born to HBeAg-positive mothers are effectively protected against HBV infection when immunized with the HBsAg vaccine. As such, Chisari et al provide sufficient motivation for one of ordinary skill in the art to apply the HBeAg to the HBsAg DNA vaccine of the combined cited references of Assateerawatt and Donnelly. With regard to Chisari misinterpreted Beasley's reference Beasley's reference is not cited in the instant combined references, of Assateerawatt, Donnelly and Chisari. In the instant case Chisari is cited to make up the deficiency for the use of more than one epitopes in the DNA vaccine of Assateerawatt, and Donnelly. One of ordinary of skill in the art would have been particularly motivated to use DNA vaccine since Donnelly concludes immunization with DNA is a simple, robust and since Chisari teaches neonates born to HBeAg-positive mothers are effectively protected against HBV infection when immunized with the HBsAg vaccine. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

***Conclusion***

**No claim is allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632